Effect of Intravenous Acetaminophen on Post-Anesthesia Care Unit Length of Stay, Opioid Consumption, Pain, and Analgesic Drug Costs After Ambulatory Surgery

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ABSTRACT

Objectives: The primary objective was to assess whether the use of intravenous acetaminophen (APAP) in the ambulatory surgery setting is associated with a decreased length of stay in the post-anesthesia care unit (PACU). The secondary outcomes evaluated were pain scores, opioid consumption, and total cost of analgesics used in the PACU.

Methods: This was a retrospective cohort study conducted in adult patients (18 years of age or older) who received an eye, ear, nose, or throat (EENT) procedure at an outpatient surgery center between January 2014 and January 2015. Patients were consecutively included until the desired sample was reached during two six-month time periods: 1) intravenous APAP available on the formulary (APAP group) and 2) intravenous APAP not available on the formulary (non-APAP group).

Results: The cohort included 174 patients who received an EENT procedure (87 patients in the APAP group and 87 patients in the non-APAP group). The median PACU length of stay was 66 minutes (interquartile range [IQR], 48–92) in the APAP group and 71 minutes (IQR, 52–89) in the non-APAP group ($P = 0.269$). Mean pain score categories in the APAP versus non-APAP group were mild (85% versus 53%, respectively; $P < 0.001$), moderate (13% versus 33%, respectively; $P = 0.002$), and severe (2% versus 14%, respectively; $P = 0.005$). The median opioid consumption in morphine equivalents was 9 mg (IQR, 5–13) in the APAP group and 8 mg (IQR, 5–12) in the non-APAP group ($P = 0.081$). The total cost of analgesics used in the PACU was significantly greater in the APAP group ($15 versus $1; $P < 0.001$).

Conclusions: Intravenous APAP use in EENT ambulatory surgery is not associated with decreased PACU length of stay. However, it may decrease postoperative pain following EENT procedures.

Keywords: acetaminophen, pain, ambulatory surgical procedures, analgesics

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INTRODUCTION

Most surgeries today are conducted in the outpatient setting.[1] From 1992 to 2012, the proportion of surgeries performed at ambulatory centers in the United States increased from 54% to 65%.[2] Historically, opioids have been the primary analgesics used for postoperative pain control in these patients. However, opioids have adverse effects, such as central nervous system and respiratory depression, which limit their use. Thus, guidelines suggest that multimodal analgesia should be used to minimize opioid consumption, increase effectiveness of postoperative analgesic therapy, and decrease drug-induced adverse effects.[3] The concept of multimodal analgesia is the simultaneous provision of different classes of analgesics with different mechanisms to produce an additive or synergistic analgesic effect.[4] Intravenous acetaminophen (APAP) is one treatment option for postoperative pain that can be used as part of a multimodal treatment regimen. Intravenous APAP does not have central nervous system or respiratory depressant properties and may reduce postoperative opioid requirements because of its analgesic effect. This has the potential to improve patient recovery after surgery.

In the ambulatory surgery setting, intravenous APAP has unique properties that make it an appealing adjunctive agent. It is relatively safe with few adverse effects, and the intravenous formulation as opposed to the oral formulation allows for drug administration soon after surgery to control postoperative pain when patients are unable to take tablets.[5] Intravenous APAP has a half-life of 2.4 hours and a dosing interval of six hours. It is theorized that the use of a single postoperative dose of intravenous APAP would enable earlier patient recovery, which would facilitate an earlier discharge from the post-anesthesia care unit (PACU).

Although previous studies have evaluated postoperative pain control and opioid consumption, none have evaluated the effect on earlier discharge from the PACU. In one trial, intravenous APAP reduced opioid consumption after outpatient sinus surgery.[6] In this study, the use of rescue analgesics (i.e., oxycodone) occurred in 71% of patients in the placebo group and only 25% of patients in the intravenous APAP group. However, the effect on length of stay was not evaluated. Most other trials have been performed in patients undergoing major surgery during hospitalization.[7–13] In hospitalized postoperative patients, some studies have shown that the use of intravenous APAP decreased pain, reduced opioid consumption,

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and resulted in a faster recovery.[10,11] But there is a gap in the literature pertaining to ambulatory surgery.

Our primary objective was to assess whether intravenous APAP use in the ambulatory surgery setting is associated with a decreased length of stay in the PACU. The usual length of stay can vary but is typically less than three hours in the ambulatory surgery setting. We hypothesized that there would be a reduced length of stay with the use of intravenous APAP. The secondary objectives were to evaluate the effect of intravenous APAP on pain scores, opioid consumption, and analgesic drug costs.

METHODS

Study Design and Setting

This was a retrospective cohort study conducted at an ambulatory surgery center affiliated with a university hospital in the United States. The surgery center did not have any written protocol in place for postoperative pain management, so analgesic provision was based on provider preference. Providers had access to opioids, ketamine, intravenous and oral APAP, lidocaine, and ketorolac. None of the patients in the study used patient-controlled analgesia in the PACU. Intravenous APAP was routinely used in all eye, ear, nose, or throat (EENT) procedures because this set of providers considered that this drug would improve recovery and decrease PACU length of stay. This was the primary rationale that EENT physicians used to justify the medication's costs and its retention on the formulary. No providers other than EENT physicians utilized intravenous APAP at the facility. In addition to intravenous APAP, pain in the PACU was primarily managed using intermittent intravenous boluses of opioids.

In July 2014, the institution removed intravenous APAP from the formulary due to a cost increase from the manufacturer. After this, all EENT procedures were performed without the use of intravenous APAP for postoperative pain. At the time of removal from the formulary, the EENT providers were notified that other analgesics, such as ketamine, lidocaine, and ketorolac, could be used instead of intravenous APAP. In addition, oral APAP could be used when possible. The university's institutional review board approved the study prior to data collection.

Patient Selection

Consecutive adult patients (at least 18 years of age) who received an EENT procedure in the ambulatory surgery center were included until the desired sample of 87 patients was reached in each group. A list of all patients who underwent a procedure was generated, and EENT procedures were identified. We selected a population of patients who received only EENT procedures to provide a relatively homogenous population. This was also the only population of patients for whom intravenous APAP was routinely used. Patients in the APAP group were included during the period when the medication was available on the formulary (January 2014 to June 2014). Patients in the non-APAP group were included during the period when it was not available on formulary (July 2014 to January 2015). Patients were included chronologically until the desired sample size was reached for each period. In other words, the first 87 patients in each period were included consecutively. There were no exclusion criteria other than the age limits and procedure type listed above.

Study Variables and Data Collection

Data were collected from electronic medical records by one of the investigators and entered into an online data capture system using a standardized form. Research Electronic Data Capture (REDCap) was used for data collection. Data collected included demographics, comorbidities, surgery type, pain scores, analgesic consumption (opioid and nonopioid), adverse effects, and PACU length of stay. Pain was measured on a numerical rating scale of 0 to 10 (0 = no pain, 10 = worst possible pain). We collected all pain scores documented in the PACU after administration of intravenous APAP, which was given immediately after surgery. The mean pain score was then calculated and used for analysis. Three or more scores were documented for most patients. The only nonsteroidal anti-inflammatory agent used in these patients was intravenous ketorolac. All opioids were converted to intravenous morphine equivalents for our outcome of opioid consumption in the PACU. The institution's average acquisition cost was used to derive total analgesic cost in the PACU, with all costs represented in 2014 U.S. dollars.

Data Analysis

Continuous data were reported as means with standard deviations if normally distributed. Data that were not normally distributed were reported as medians with interquartile ranges (IQRs). The distribution of data for each variable was evaluated visually via histograms. Because length of stay is typically skewed, this variable was also reported as medians. An unpaired Student's *t*-test or the Wilcoxon rank-sum test was used to compare continuous data between groups as appropriate. Categorical data were reported as percentages and compared between groups using the Fisher's exact test or *chi*-square test as appropriate. The mean pain scores were highly skewed, thus this variable was categorized as mild pain (score 0–3), moderate pain (score 4–6), and severe pain (score 7–10). An *a priori* alpha of 0.05 was used for all analyses. All data analyses were conducted in Stata 13 (StataCorp LP, College Station, Texas).

Based on previous studies conducted in outpatient surgery settings, we considered a mean PACU length of stay of approximately 120 minutes for the APAP group and 150 minutes for the non-APAP group with a common standard deviation of 70 minutes.[14] This reduction of 30 minutes was based on what we considered to be clinically meaningful and on estimates of the EENT providers at our institution to justify the use of intravenous APAP. Using an alpha of 0.05 and power of 80%, we established a sample size of 87 patients in each group.

RESULTS

The overall cohort included 87 patients who received intravenous APAP in the PACU and 87 patients who did not receive intravenous APAP. Because the initial list we obtained included only EENT ambulatory surgeries, no patients were excluded. The mean age was 49 ± 19 years, 94 patients (54%) were men, and mean weight was 81 ± 19 kg. Comparisons between groups with regard to demographic and clinical variables appear in Table 1 along with the types of EENT surgeries performed. The two groups were similar with respect to demographic categories and most comorbid conditions. There were more patients

Table 1 Demographic and Clinical Data

	APAP (n = 87)	Non-APAP (n = 87)	*P* Value
Demographics			
Age (mean ± SD)	46 ± 20	51 ± 19	0.13
Weight (kg) (mean ± SD)	79 ± 19	83 ± 18	0.20
Male (n [%])	44 (51)	50 (58)	0.45
Comorbid conditions (n [%])			
Heart failure	3 (3)	0 (0)	0.25
Coronary artery disease	6 (7)	16 (18)	0.04
Diabetes	10 (12)	12 (14)	0.82
Chronic obstructive pulmonary disease	2 (2)	10 (12)	0.03
Asthma	18 (21)	17 (20)	1.00
Chronic kidney disease	2 (2)	3 (4)	1.00
Chronic pain condition	23 (26)	16 (18)	0.28
Depression	12 (14)	10 (12)	0.82
Bipolar/psychosis	2 (2)	6 (7)	0.28
Anxiety disorder	6 (7)	18 (21)	0.01
Fibromyalgia	0 (0)	1 (1)	1.00
Diabetic neuropathy	1 (1)	0 (0)	1.00
Cancer	6 (7)	10 (12)	0.43
Procedures (n [%])			
Cataract surgery	10 (12)	4 (5)	0.16
Cornea transplant/ conjunctiva excision	7 (8)	10 (12)	0.61
Entropion repair/ blepharoplasty	3 (4)	3 (4)	1.00
Rectus recession	2 (2)	9 (10)	0.06
Glaucoma valve insertion	4 (5)	1 (1)	0.37
Vitrectomy	1 (1)	1 (1)	1.00
Nasal surgery	31 (36)	30 (35)	1.00
Sinus surgery	10 (12)	20 (23)	0.07
Mastoidectomy	3 (4)	0 (0)	0.25
Ear exploration/ tympanoplasty	3 (4)	0 (0)	0.25
Tonsillectomy	8 (9)	4 (6)	0.37
Other	1 (1)	2 (2)	1.00
Adjunctive analgesics (n [%])			
Ketorolac	12 (14)	10 (12)	0.82
Oral acetaminophen	7 (8)	34 (29)	< 0.01
Ketamine	9 (10)	1 (1)	0.02
Lidocaine	27 (31)	72 (83)	< 0.01

APAP = intravenous acetaminophen

with coronary artery disease, chronic obstructive pulmonary disease (COPD), and anxiety disorders in the non-APAP group than in the APAP group. The majority of patients in the APAP group received 1,000 mg APAP intravenously as a single dose (n = 84 of 87, 97%). None of the patients in the study had respiratory depression requiring the use of naloxone.

The median PACU length of stay was 66 minutes (IQR, 48–92) in the APAP group and 71 minutes (IQR, 52–89) in the non-APAP group ($P = 0.269$) (Table 2). Mean pain score categories in the APAP versus non-APAP groups were mild (85% versus 53%, respectively; $P < 0.001$), moderate (13% versus 33%, respectively; $P = 0.002$), and severe (2% versus 14%, respectively; $P = 0.005$). The median opioid consumption in intravenous morphine equivalents was 9 mg (IQR, 5–13) in the APAP group and 8 mg (IQR, 5–12) in the non-APAP group ($P = 0.081$). The use of some adjunctive medications differed between the APAP and non-APAP groups. Intravenous lidocaine (31% versus 83%; $P < 0.001$) and oral APAP (8% versus 29%; $P < 0.001$) were used less in the intravenous APAP group compared with the non-APAP group. The median dose of lidocaine used was 100 mg (IQR, 90–100). Ketamine was used more often in the APAP group (9%) versus the non-APAP group (1%) ($P = 0.018$). The median dose of ketamine used was 50 mg (IQR, 30–50). Intravenous ketorolac use was similar in the APAP (14%) and non-APAP groups (12%) ($P = 0.820$). With the exception of three patients who received ketorolac 15 mg, all patients received a single dose of 30 mg. There was no use of other nonsteroidal anti-inflammatory agents or any rectal APAP. The total cost of analgesics used in the PACU was significantly greater in the APAP group compared with the non-APAP group ($15 versus $1; $P < 0.001$).

DISCUSSION

The key finding of this study is that the use of intravenous APAP in the PACU did not reduce length of stay in patients undergoing EENT surgery at our institution. The primary rationale of the providers for use of intravenous APAP in this setting was that it would reduce opioid consumption in the

Table 2 Results

	APAP (n = 87)	Non-APAP (n = 87)	*P* Value
Post-anesthesia care unit length of stay in minutes (median [IQR])	66 (48–92)	71 (52–89)	0.27
Pain score categories (n [%])*			
Mild (0–3)	73 (85)	46 (53)	< 0.01
Moderate (4–6)	11 (13)	28 (33)	< 0.01
Severe (7–10)	2 (2)	12 (14)	< 0.01
Opioid consumption (intravenous morphine equivalents in milligrams) (median [IQR])	9 (5–13)	8 (5–12)	0.08
Total cost of analgesics ($) (median [IQR])	15 (14–16)	1 (1–3)	< 0.01

APAP = intravenous acetaminophen; IQR = interquartile range.

* Pain was measured on a numerical rating scale of 0 to 10 (0 = no pain, 10 = worst possible pain). One patient in each group had missing pain scores.

PACU and thus decrease recovery time, enabling patients to be discharged home sooner.[1] However, our findings suggest that opioid consumption was not reduced, and PACU length of stay was similar between groups. A significant finding is that the use of intravenous APAP was associated with better pain control in the PACU. There were also greater analgesic drug costs associated with the use of intravenous APAP ($15 versus $1). This was primarily attributed to the cost of intravenous APAP. The drug's cost doubled at our institution, which led to its removal from the formulary. Thus, this disparity in drug costs is expected to be greater today than reported in our study.

In a previous randomized controlled study (N = 74) conducted in patients undergoing endoscopic sinus surgery, patients received a single dose of 1 g intravenous APAP or placebo.[6] Within four hours after surgery, fewer patients in the APAP group required rescue opioid analgesia (25% versus 71%; $P = 0.001$). There were also fewer patients in the APAP group who reported significant pain (31% versus 58%; $P = 0.018$). The authors defined this as a score greater than 3 on 0–10 numerical rating scale at any time during the study. In our study, we showed a reduction in pain, but opioid consumption was not reduced. This could result from differences in the types of EENT procedures in our population or differences in the use of other adjunctive analgesics.

The use of intravenous APAP has been studied after a variety of surgeries, such as abdominal, cardiac, orthopedic, dental, otolaryngologic, and others.[15] However, the evidence is greatest for major surgeries, such as those involving the abdomen. In one systematic review involving seven randomized controlled trials, intravenous APAP was associated with an opioid-sparing effect, involving a 20% reduction in morphine use via patient-controlled analgesia.[10] However, it did not reduce morphine-related adverse effects. Some studies have shown a decrease in hospital length of stay with the use of intravenous APAP.[8,16] In patients undergoing abdominal hysterectomy, the mean hospital length of stay was decreased from 6.4 days to 5.2 days ($P < 0.05$).[8] Similarly, in patients undergoing laparoscopic colorectal resection, mean hospital length of stay decreased from five days to three days ($P < 0.05$). However, these trials have been conducted in European countries, limiting extrapolation to the United States because of different processes and conditions that determine eligibility for discharge. Our study is unique because it was in a population that has not been studied as extensively. Given the increasing trend toward ambulatory surgery, this study helps evaluate the use of intravenous APAP in a population where there is increasing interest in its utilization. When the decision was made to remove intravenous APAP from the formulary due to budgetary implications, proponents for its use argued that the increase in cost was justified because the medication decreased resource use by reducing PACU length of stay. We did not see an increased length of stay after intravenous APAP's removal from the formulary. This suggests that other adjunctive agents (e.g., oral APAP, lidocaine, ketorolac, ketamine) may be adequate as part of multimodal regimens in this setting. However, the increase in pain scores that occurred after removal of intravenous APAP from the formulary is concerning.

The study has a few important limitations inherent in the retrospective design. The study was conducted in a single institution in the United States, which may limit the generalization of these results. There was an imbalance between groups with regard to a few comorbidities, such as coronary artery disease, COPD, and anxiety disorder. Patients in the non-APAP group were more likely to have anxiety disorder, which has the potential to influence pain and opioid consumption.[17] However, the comorbidities we considered to be most important pertained to the presence of chronic pain conditions, which were similar between groups. There were also differences between groups with regard to the use of adjunctive analgesic agents. For instance, the intravenous APAP group was less likely to receive oral APAP. This is intuitive because after removal of intravenous APAP from the formulary, the staff was provided with information regarding available alternatives, such as oral APAP. A few patients in the intravenous APAP group also were more likely to receive intravenous ketamine, and patients in the non-APAP group were more likely to receive intravenous lidocaine. Although the increased use of lidocaine was expected, the decrease in the use of ketamine was surprising. However, it should be noted that there were very few patients overall who received ketamine, and this difference could be attributed to random variation. This occurred because the staff decided to use other intravenous options instead of APAP. We can only speculate regarding how these differences affected pain scores and opioid consumption. It is possible that the use of these other adjunctive agents instead of intravenous APAP resulted in minimizing potential differences in length of stay. We did not collect information regarding the timing of pain scores in the PACU. Thus we could not plot the time course of pain to gain a better understanding for this measure in the PACU. However, because the stay in the PACU is only for a few hours, we did not consider this to be necessary. At the time of the study there was no protocol in place for postoperative pain, and this management was at the discretion of the physician. As a result, there could have been variation among patients with regard to their analgesic provision. However, we have no reason to believe that this variation would be any different between the two study phases. We did not collect data regarding providers, which would have influenced the selection of analgesics. Finally, we considered PACU length of stay to be more meaningful as an outcome than discharge from the surgical center. This is because PACU length of stay influences throughput in the surgical center. Discharge from the surgical center itself can be attributed to nonmedical issues, such as availability of transport, so it was not used as our outcome.

CONCLUSION

Intravenous APAP use in ambulatory surgery patients undergoing EENT procedures is not associated with decreased PACU length of stay. However, intravenous APAP may decrease postoperative pain in this setting. Analgesic drug costs are significantly greater when intravenous APAP is used.

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